A Novel Microenvironment-Mediated Functional Skeletal Muscle from Human Embryonic Stem Cells and their In Vivo Engraftment

Grant Award Details

A Novel Microenvironment-Mediated Functional Skeletal Muscle from Human Embryonic Stem Cells and their In Vivo Engraftment

Grant Type: New Faculty II

Grant Number: RN2-00945

Project Objective: Ultimate goal is to generate large numbers of human myogenic progenitors(hopefully satellite cells) by employing the PIs material expertise and test their efficacy in a model of Duchenne's muscular dystrophy.

Investigator:

Name:	Shyni Varghese
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Muscular Dystrophy, Skeletal/Smooth Muscle disorders

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $2,300,569

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5

View Report

Reporting Period: NCE Year 6

View Report

Grant Application Details

Application Title: A Novel Microenvironment-Mediated Functional Skeletal Muscle from Human Embryonic Stem Cells and their In Vivo Engraftment

Public Abstract: Muscle wasting is a serious clinical problem associated with a number of diseases and health conditions, affecting individuals of all ages. Muscular dystrophy (MD) is a form of muscle wasting disease resulting from genetic mutations. Duchenne muscular dystrophy (DMD) is the most common form of MD that limits motility and life expectancy of children. It is characterized by progressive skeletal muscle degeneration, and occurs in 1 out of every 3,500 male births. Currently, there is no effective treatment to stop or reverse DMD. One of the potential clinical solutions for treating DMD is cell transplantation where the implanted cells contribute to the functional muscle regeneration. Adult stem cells such as mesoangioblasts and AC133 cells have already been shown to ameliorate dystrophic muscle pathology in animals. Although embryonic stem cells (ESCs) can provide unlimited numbers of progenitor cells with the ability to contribute to the formations of functional skeletal muscle, their ability to reverse/repair wasting muscle has not been explored in detail. To this end, we seek to develop an ESC-based cell transplantation therapy for treating muscle-wasting pathology, focusing on DMD. Three specific aims are proposed to achieve this overall goal. (i) Optimize the microenvironment factors comprising of cell-matrix interaction, cytokines, and cell-secreted morphogens on differentiation of ESC into muscle cells using a combinatorial array technology. (ii) Derive and characterize a population of clinically viable ESC-derived muscle progenitor cells using a dynamic, three-dimensional (3D), bioengineered niche. The tailored niche would be comprised of a multifunctional hydrogel that exhibits “excitation-contraction” dynamics. We will then functionalize this hydrogel with optimized ECM components and use it to investigate myogenic differentiation of ESCs in a 3D environment, and to derive engraftable muscle progenitor cells from ESCs. (iii) Investigate the therapeutic efficacy of ESC-derived progenitors for treating DMD pathology using animal models. The molecular pathways involved in myogenic differentiation of ESCs will be analyzed using proteomics and transcriptomics tools. Successful completion of this study could offer broad applicability of stem-cell-based therapies for treating all types of muscle wasting diseases and other pathologies associated with dysfunctional muscles. Unraveling the microenvironment factors and molecular events determining the commitment of ESCs into specific lineages will significantly increase our understanding of stem cell biology and their application in regenerative medicine. In addition, the multifunctional hydrogel (mechanical actuator) developed here could find many applications in the field of artificial functional implants where a muscle-like response is desirable, cardiac tissue repair, drug delivery, and biomimetic devices.

Statement of Benefit to California:	The proposed study seeks to develop a clinically viable cell transplantation therapy based on pluripotent embryonic stem cells (ESCs) for treating muscular dystrophies (MDs), especially Duchenne muscular dystrophy (DMD). DMD is the most common form of MD that limits motility and shortens life expectancy of children, and is estimated to occur 1 in 3500 male births. DMD is characterized by progressive muscle wasting, limited ambulation, compromised lung or cardiac function, paralysis, and ultimately premature death. DMDfund (http://www.dmdfund.org), a California-based forum dedicated to families of children affected by DMD, emphasizes the devastating nature of this disease "... in contrast to cancer, DMD currently is uniformly fatal. As a result there is only a 3-fold difference in the number of childhood deaths due to cancer vs. DMD, but DMD research is relatively scarce. The paucity of research may be the reason that there is no cure for this devastating neuromuscular disease. Without research, there is no hope. Shouldn't all people at least been given the chance to hope?" Clearly, there is a need to develop new paradigms for treating DMD. The PI has proposed one possible approach to address this need and it will contribute to the State of California and its citizens in the many ways: Clinical benefits: Successful completion of the project will help develop new stem-cell-based therapies for treating DMD and other muscle wasting diseases. Unraveling the microenvironment factors and molecular events that determine the commitment of ESCs will significantly increase their treatment potential. Concepts and knowledge gained from the study can translate into other areas of regenerative medicine. Economic benefits: There are two ways the proposed work could contribute to the economy of California. First, improvements in DMD treatment could bring down the healthcare costs. Second, tools and technologies developed during the course of this study (soft mechanical actuators, smart biomimetic hydrogels, etc.) can find various other applications in biomedical fields such as artificial functional implants, cardiac tissue repair, drug delivery, and biomimetic devices. Such devices could be of great interest to California-based biotechnology companies. The PI's past work involving musculoskeletal tissues has contributed to a start-up biotech company located in California, and the PI hopes to contribute similarly through the proposed studies. Education, training, and awareness: One of the most important components of the PI's laboratory is training future leaders in the biomedical/stem cell field. We expect to train 10-12 researchers within the course of this project (clinical fellows, postdoctoral fellows, graduate students, undergraduate students, and high school students). These very students and trainees will, in the future, lead to the development of newer and more advanced strategies for regenerative medicine.

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